Remarks

Reconsideration of this Application is respectfully requested.

Claims 9-16 and 21 are pending in the application. All the claims stand rejected.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 9-12, 14-16 and 21 under 35 U.S.C. § 102(b) as allegedly anticipated by Scott *et al.*, *J. Biol. Chem.* 271:1605-12 (1996). (Paper No. 18, page 2.) Applicants respectfully traverse the rejection.

Claim 9 is directed to "[a] nucleic acid molecule encoding a *mammalian* signal peptide operatively linked to a nucleic acid encoding a protein that would normally not be secreted from a mammalian cell, said signal peptide allowing at least some of said protein to be synthesized on the endoplasmic reticulum in a manner *so that said protein can be secreted* . . . ." (emphasis added.) Thus, the claim requires that the signal peptide be mammalian and that it direct the protein to the endoplasmic reticulum so that is can be secreted. According to the specification, the signal peptide can be derived from, for example, rat albumin, bovine growth hormone, lactalbumin and other milk proteins. (Specification, page 3, lines 11-12.)

In contrast, Scott *et al.* use a signal sequence which is *not* mammalian. Rather, as shown at page 1608, second column, last paragraph, the signal sequence used in Scott *et al.* is the *influenza virus* HA signal sequence. In addition, the signal sequence in Scott *et al.*

does *not* allow secretion of the protein. For example, the abstract states that "[t]he addition of a conventional signal peptide to the amino terminus of PI-6 directed its translocation into the endoplasmic reticulum (ER), resulting in glycolsylation but not secretion of the molecule." Moreover, page 1609, first column, first full paragraph states that "[t]he number and sizes of these proteins did not alter during the 3-h chase period, and none were detected in the media, suggesting that HA/PI-6 cannot exit the secretory pathway" and page 1609, second column, second full paragraph states "[t]he failure to detect secretion of the HA/PI-6 glycoforms (Fig. 6) suggested that they are trapped somewhere along the secretory pathway." Accordingly, Scott *et al.* does not teach every element of the claims.

With respect to the Examiner's assertion that "one of ordinary skill in the art would immediately envision the RNA sequence given the cDNA sequence of Scott et al.," Applicants submit that this contention, seemingly referring the dependent claim 11, is irrelevant given that Scott *et al.* does not teach every element of the independent claim.

Moreover, as pointed out on numerous previous occasions, the present invention is based on the finding that efficient secretion of mammalian proteins can be achieved by making a deletion, insertion or substitution in respect to the native 3'-UTR of the nucleic acid encoding the mammalian protein. There is simply nothing in Scott *et al.* which suggests that secretion of PI-6 can be achieved by altering the 3'-UTR of the PI-6 gene. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 12 and 13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Scott *et al.* in view of Sleep *et al.*, *Biotechnology* 8:42-46 (1990). (Paper No. 18, page 3.) Applicants respectfully traverse the rejection.

Initially, Applicants point out that the Examiner has rejected claims 12 and 13 under 35 U.S.C. § 103(a) for obviousness, but not claim 9. As the Examiner appears to consider claim 9 patentable and claims 12 and 13 depend on claim 9, then claims 12 and 13 must also be patentable.

The defects of Scott *et al.* have been explained above. As discussed, Scott *et al.* describe an influenza virus HA signal sequence which did not result in secretion of PI-6. The Examiner appears to believe that "Sleep et al. do teach the use of a human serum albumin signal sequence to secrete a protein." (*Id.*) While this may be true, the HSA protein taught in Sleep *et al.* is a protein that is, in fact, normally secreted. This is in contrast to the claims which require that the protein "normally not be secreted from a mammalian cell." In addition, Sleep *et al.* relate to secretion in yeast cells rather than mammalian cells.

There is no suggestion in either Scott *et al.* or Sleep *et al.* to use a different signal sequence other than the one described in the respective reference. Scott *et al.* use HA to study whether or not PI-6 can be secreted. There is absolutely no suggestion to use other signal peptides to characterize PI-6. Sleep *et al.* studied the effect of five specific signal sequences on the secretion of human serum albumin (HSA), a protein that is normally secreted. Sleep *et al.* state at page 45, column 1, second full paragraph, that "[t]he high efficiency of all these leader systems in directing the secretion of HSA is likely to reflect the nature of HSA as a protein in that it is a naturally secreted product. . . ." Given the positive

results, there is no suggestion or teaching in Sleep *et al.* to use other signal sequences. Moreover, there is no suggestion in either reference to use a different protein other than the one being studied in each respective reference. The focus of Scott *et al.* is characterizing PI-6 and the focus of Sleep *et al.* is secreting HSA in yeast cells.

Regarding the expectation of success in combining the two references, the Examiner has stated that:

> [o]ne of ordinary skill in the art would have had a reasonable expectation of success in substituting human serum albumin signal sequence of Sleep et al., for the HA signal sequence of Scott et al. since molecular cloning techniques were well-known and highly successful at the time of the present invention, as evidenced by their successful use by Scott et al. and Sleep et al.

(Paper No. 18, page 3.) Applicants respectfully disagree.

Although molecular cloning techniques were well-known, there was not a reasonable expectation of success that operatively linking a given signal sequence to a specific protein that is not normally secreted would result in secretion. This fact is supported by the results of Scott *et al.* who, as discussed above, disclose that the signal sequence of the influenza HA protein did *not* result in secretion of PI-6.

Finally, Applicants again emphasize that the crux of the invention is the unexpected finding that efficient secretion of mammalian proteins can be obtained by making a deletion, insertion or substitution in the 3'-UTR of the native nucleic acid encoding the mammalian protein. There is absolutely no teaching in either Scott *et al.* or Sleep *et al.* which suggests considering the effects that altering the 3'-UTR might have on the efficiency of secretion. Thus, the combination of references do not teach or suggest every element of the claims.

Indeed, the Examiner appears to have completely ignored this aspect of the invention in his remarks.

In view of the above, Applicants assert that the cited references do not render the claims unpatentable. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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